■ SPINE

# Gelatine matrix with human thrombin decreases blood loss in adolescents undergoing posterior spinal fusion for idiopathic scoliosis

## A MULTICENTRE, RANDOMISED CLINICAL TRIAL

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### Aims
**In a multicentre, randomised study of adolescents undergoing posterior spinal fusion for idiopathic scoliosis, we investigated the effect of adding gelatine matrix with human thrombin to the standard surgical methods of controlling blood loss.**

### Patients and Methods
**Patients in the intervention group (n = 30) were randomised to receive a minimum of two and a maximum of four units of gelatine matrix with thrombin in addition to conventional surgical methods of achieving haemostasis. Only conventional surgical methods were used in the control group (n = 30). We measured the intra-operative and total blood loss (intra-operative blood loss plus post-operative drain output).**

### Results
**Each additional hour of operating time increased the intra-operative blood loss by 356.9 ml (p < 0.001) and the total blood loss by 430.5 ml (p < 0.001). Multiple linear regression analysis showed that the intervention significantly decreased the intra-operative (-171 ml, p = 0.025) and total blood loss (-177 ml, p = 0.027). The decrease in haemoglobin concentration from the day before the operation to the second post-operative day was significantly smaller in the intervention group (-6 g/l, p = 0.013) than in the control group.**

### Conclusion
**The addition of gelatine matrix with human thrombin to conventional methods of achieving haemostasis reduces both the intra-operative blood loss and the decrease in haemoglobin concentration post-operatively in adolescents undergoing posterior spinal fusion for idiopathic scoliosis.**

**Take home message: A randomised clinical trial showed that gelatine matrix with human thrombin decreases intra-operative blood loss by 30% when added to traditional surgical haemostatic methods in adolescents undergoing posterior spinal fusion for idiopathic scoliosis.**

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Surgery for adolescent idiopathic scoliosis (AIS) can be associated with major blood loss.[1-3] Predictors of the need for allogeneic blood transfusion in these patients are the use of a posterior approach, patients in whom nine or more levels are to be fused and those with additional comorbidities.[3] Bleeding from highly vascular paraspinal muscles, cancellous bone or epidural venous plexus may require allogeneic or autologous blood transfusions, given that most patients with adolescent idiopathic scoliosis typically undergo posterior spinal fusion of nine or more levels.[3,4] Peri-operative allogeneic blood transfusion increases the risk of post-operative infection and transfusion reactions which may slow post-operative recovery.[5-7]

Randomised clinical trials have shown that using a gelatine matrix with thrombin to assist haemostasis decreases the operating time and intra-operative blood loss of patients undergoing cardiac,[8] general,[9,10] and ENT surgery.[11,12] There are, however, few randomised clinical trials on its use in orthopaedic or spinal surgery. Renkens et al[13] randomised 127 adult patients undergoing spinal surgery, who failed to

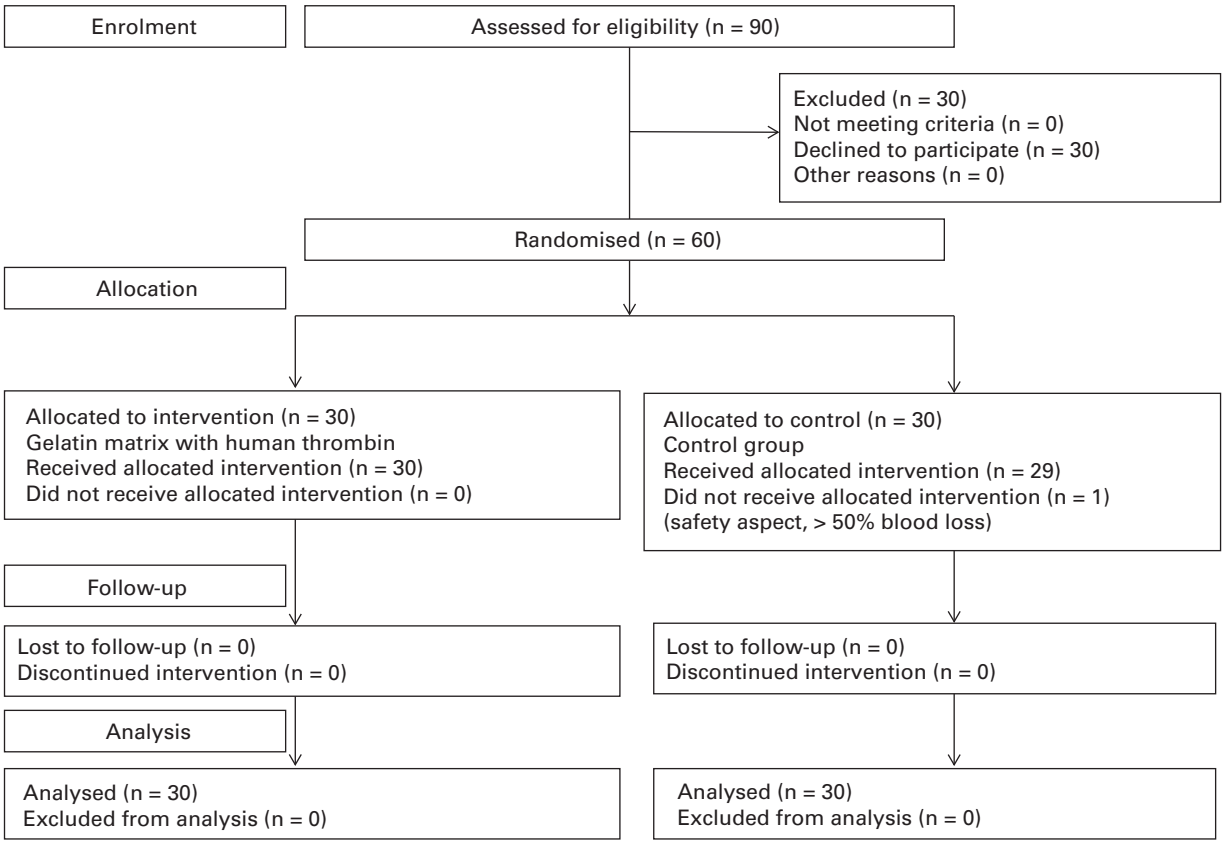


Fig. 1

Consolidated Standards of Reporting Trials (Consort) [24] flow chart.

respond to conventional surgical means of controlling bleeding, into two groups one of which received gelatine matrix with bovine thrombin and the other Gelfoam (Pfizer, New York City, New York) soaked in bovine thrombin. They found that bleeding was controlled faster with the gelatine matrix sealant: 98% of patients who received this product stopped bleeding within ten minutes compared with 90% of the Gelfoam group.

Two randomised clinical trials have shown reduced intra-operative blood loss in patients undergoing total knee arthroplasty.[14,15] The effects on post-operative drainage are controversial. Some studies have shown reduced blood loss[14,15] and another no effect.[16] There have also been two studies in children undergoing adenoidectomy or adenotonsillectomy, in which it was shown that gelatine matrix reduced both intra-operative blood loss and operating time.[11,12] In addition to increased cost, the use of gelatine matrix has been associated with rare but severe peri-operative complications.[17-20] Anaphylaxis has occurred during posterior[17] and anterior surgery for spinal deformity.[18] There have also been two reports of epidural spinal cord compression with neurological deficits. Both of these were associated with the intrapedicular application of gelatine matrix during pedicle screw insertion. Both needed urgent surgical evacuation of intraspinal haematoma.[19]

Although there have been no clinical trials of gelatine matrix with human thrombin in paediatric orthopaedic surgery, it has been widely used in children undergoing surgery for spinal deformity.[4,17,19,21-23] It has been applied topically to enhance haemostasis when conventional surgical techniques have failed or were difficult to apply.

The purpose of this randomised trial was to verify the efficacy of adding gelatine matrix to conventional surgical methods of addressing blood loss in adolescents undergoing surgical correction of an idiopathic scoliosis. We hypothesised that gelatine matrix with human thrombin would be more effective at reducing operative blood loss than conventional surgical methods alone.

## Patients and Methods

**Study design**. We conducted a randomised, multicentre, clinical trial according to CONSORT criteria[24] at three major university hospitals in Finland. The trial was registered at ClinicalTrials.gov (NCT01451788).

Ethical permission was obtained from the Ethics Committee of the primary hospital at which the study was conducted. All patients gave their informed consent.

The study was carried out between January 2012 and December 2014. The trial ended when all patients had been enrolled and operated on and had completed follow-up by December 2014.

**Table I.** Baseline characteristics of enrolled patients

| Parameter* | Control group (n = 30) | Treatment (n = 30) | p-value |
|---|---|---|---|
| Age at surgery (yrs) | 15.4 (2.1) | 16.0 (2.1) | 0.28 |
| Gender (M:F) | 7:23 | 10:20 | 0.34 |
| BMI | 19.9 (3.3) | 20.6 (3.0) | 0.42 |
| Type of scoliosis (n) | | | 0.16 |
| AIS | 26 | 29 | |
| JIS | 4 | 1 | |
| Lenke type (n)† | | | |
| 1 | 10 | 9 | |
| 2 | 11 | 10 | |
| 3 | 2 | 1 | |
| 4 | 2 | 0 | |
| 6 | 5 | 10 | |
| Estimated blood volume (mls) | 3890 (666) | 4017 (731) | 0.49 |
| No. of levels fused | 11.1 (1.3) | 11.4 (1.4) | 0.40 |
| No. of Ponte procedures | 10 | 9 | 0.70 |
| No. of screws placed | 21.9 (3.0) | 22.1 (2.6) | 0.78 |
| SRS-24 total score‡ | | | |
| Pre-operative | 4.4 (0.40) | 4.3 (0.53) | 0.20 |
| 6 months | 3.8 (0.41) | 3.9 (0.44) | 0.45 |

* The values are given as the mean, with the standard deviation in parenthesis
† Lenke classification for adolescent idiopathic scoliosis[25]
‡ SRS-24, Scoliosis Research Society 24 outcome questionnaire[26]
BMI, body mass index

The two treatment groups consisted of adolescents undergoing posterior surgery for an idiopathic scoliosis of between 45° and 90°.

Patients were included if they fulfilled the following criteria: between ten and 21 years of age; no contraindication to the use of gelatine matrix with human-derived thrombin; suitable for posterior scoliosis surgery using a total pedicle screw technique for AIS (Lenke classification[25] Types 1 to 4 or 6); normal blood coagulation; a normal whole spine MRI except for the spinal deformity (juvenile or AIS) (Fig. 1).

Exclusion criteria were the need for anteroposterior surgery; the need for vertebral resection; smoking; diabetes mellitus or abnormalities in blood coagulation. Pre-operative donation of autologous blood was not undertaken in any patient and use of non-steroidal anti-inflammatory medication was not recommended within one week of surgery.

The intervention group received gelatine matrix with human derived thrombin (FloSeal, Baxter United States, Deerfield, Illinois) while the control group did not. Otherwise, conventional methods of haemostasis (bone wax; bipolar diathermy and epidural space packing for epidural venous bleeding) were used.

Randomisation to intervention and control groups (1:1) was carried out using the sealed envelope technique after the induction of general anaesthesia.

The main outcome measures were intra-operative blood loss (mls), drain output over 24 hours (mls), and total blood loss (intra-operative blood loss + drain output). Secondary outcome factors included the need for blood products (packed red cells, frozen plasma or platelets), laboratory measurements (haemoglobin (Hb), haematocrit (Hct)), operating time, radiological outcomes, hospital stay and complications.

**Intervention** . The gelatine matrix with human derived thrombin (500 IU/ml) (FloSeal, Baxter United States) comes in units of 5 ml. In the treatment group, the mean number of units used to stop bleeding was 3.4 (2 to 6). It was systematically injected into every bleeding pedicle, into the epidural space in patients who were undergoing the Ponte procedure[26] and onto decorticated bony surfaces. After haemostasis had been achieved, the excess gelatine matrix not involved in formation of the clot was gently washed away from both the pedicles and the epidural space with saline. This took place typically after a minimum of two minutes or at the end of the procedure. The posterior decorticated bony elements were not irrigated. For ethical reasons, the gelatine matrix with human thrombin was used in both the treatment and control groups when bleeding exceeded 50% of the total blood volume during surgery, or if it was considered clinically to be in the best interest of the patient.

**Patients**. A total of 60 patients were enrolled in the study (Table I, Fig. 1). Pre-operative clinical examination was undertaken by one of four paediatric spinal surgeons. All patients were operated by these same spinal surgeons. Standing posteroanterior and lateral radiographs of the whole spine were taken pre-operatively and at discharge. At least two independent observers who were unaware of the chosen treatment measured the radiographs. Bending radiographs of the spine were taken pre-operatively to identify structural curves.[25] The SRS-24 questionnaire[27] was completed by the patients both pre-operatively and before discharge. All patients underwent an MRI of the whole spine

**Table II.** Radiological outcome

| Parameter* | Control | Treatment | p-value |
|---|---|---|---|
| **Upper thoracic curve (°)** | | | |
| Pre-operative | 24 (9.5) | 22 (11) | 0.64 |
| At discharge | 8.6 (5.0) | 8.2 (5.3) | 0.77 |
| Correction (%) | 61 (22) | 62 (53) | 0.89 |
| **Main thoracic curve (°)** | | | |
| Pre-operative | 52 (8.5) | 48 (12) | 0.14 |
| On bending radiograph | 40 (9.2) | 32 (15) | 0.033 |
| Curve correction (%) | 25 (14) | 26 (24) | 0.049 |
| At discharge | 12 (4.1) | 12 (5.5) | 0.96 |
| Correction (%) | 78 (7.2) | 75 (10) | 0.35 |
| **Lumbar curve (°)** | | | |
| Pre-operative | 38 (15) | 38 (13) | 0.93 |
| At discharge | 12 (7.5) | 11 (8.1) | 0.58 |
| Correction (%) | 67 (15) | 72 (19) | 0.33 |
| **Thoracic kyphosis (Th5-Th12, (°))** | | | |
| Pre-operative | 16 (11) | 23 (10) | 0.10 |
| At discharge | 19 (6.7) | 18 (7.0) | 0.52 |
| **Lumbar lordosis (T12-S1, (°))** | | | |
| Pre-operative | 49 (12) | 51 (11) | 0.59 |
| At discharge | 49 (10) | 47 (10) | 0.46 |

* The values are given as means, with the standard deviation in parentheses

and a standard coagulation profile (Hb, Hct, thrombocyte counts, prothrombin time, INR and activated partial thromboplastin time). Arterial blood sampling for Hb concentration was carried out both during and at the end of the procedure. The same blood tests were repeated on post-operative days 1 to 5.

**Surgical technique**. Surgical planning of implant placement and the need for the Ponte procedure[26] were carried out before randomisation. Each patient was placed in the prone position and the posterior elements were exposed using electrocautery. The deformity was corrected using bilateral segmental pedicle screw instrumentation and *en bloc* vertebral column derotation (6.35 CD Legacy or Solera 6.0, Medtronics Spinal and Biologics, Memphis, Tennessee).[4] Spinal fusion was carried out using autograft acquired from facetectomies and osteotomies with bone graft extenders (BCP and Nanostim, Medtronics Spinal and Biologics). Spinal cord monitoring (MEP, SSEP, lumbar nerve root EMG with or without pedicle screw stimulation) was undertaken in all patients. A single subfascial drain (Hemovac Ch14; Zimmer, Warsaw, Indiana) was routinely placed during closure and removed at 24 hours post-operatively.

**Anaesthesia**. All patients had a general anaesthetic which included dexmedetomidine, propofol and remifentanil with the aim of achieving a mean arterial pressure of between 65 mmHg and 75 mmHg during surgery and for the first 24 hours post-operatively. Cefuroxime and Vancomycin were used as antibiotic prophylaxis.

All patients received an intravenous bolus of tranexamic acid (30 mg/kg, maximum dose 1500 mg) within 30 minutes before incision and then an infusion (10 mg/kg/h, maximum dose 500 mg/h) during surgery. Intra-operative blood loss was measured and recorded as the amount of blood collected in the cell saver, surgical wound dressings were weighed during surgery, but excluding any irrigation with saline. The cell saver was used in all patients and the amount of autologous blood returned was measured. Allogeneic red blood cells were transfused if the Hb concentration was below 90 g/L during surgery or during the hospital stay. Fresh frozen plasma was given if the blood loss exceeded 50% of the patient's total blood volume. Platelets were infused if the blood loss was more than 100% of the blood volume. The estimated blood volume was calculated using a formula of 70 ml/kg x weight (kg).[28]

**Statistical analysis**. Values are given as means with standard deviations. A two-tailed independent *t*-test was used to calculate the level of significance for continuous variables (unpaired for between and paired for within group comparison). The chi-squared test was used for categorical variables.

The risk factors for bleeding (intra-operative and total blood loss, in mls) were also analysed using a multiple linear regression model (IBM SPSS statistics v21.0). All clinically relevant risk factors were analysed in a multivariate model. Only significant risk factors and the number of operated pedicles were left in the final multivariate model. A p-value < 0.05 was considered statistically significant.

The sample-size requirement of 30 patients per group was calculated using a study power of 80%, a type I error (alpha) of 0.05, and an estimated effect size of 0.7. Effect size evaluation was based on the assumption that mean (SD) peri-operative blood loss (the primary endpoint) would be 1000 (SD 600) for the control group and 600 (SD 600) for the treatment group.[4,29]

If the surgical procedure could not be performed safely on a patient in the control group without the use of gelatine matrix with human thrombin, i.e., >50% intra-operative blood loss or based on the surgeon's judgment, its use was allowed, however, the patient remained in the control

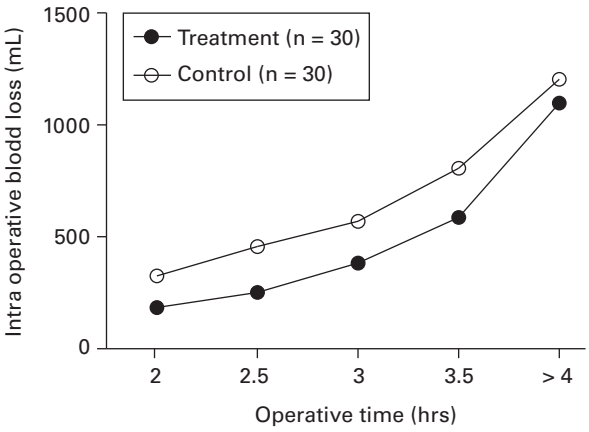


Fig. 2a

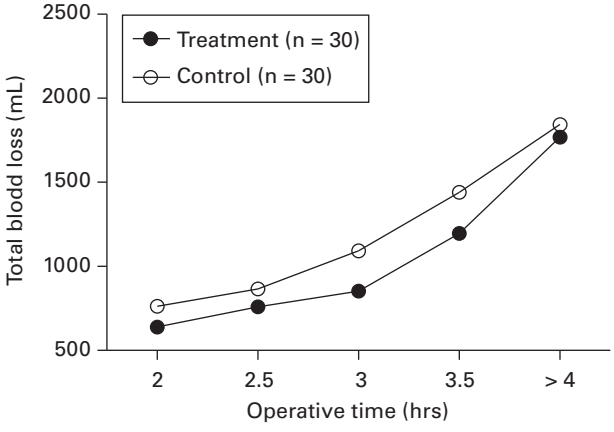


Fig. 2b

Graphs showing the effect of gelatine matrix with thrombin on bleeding in adolescents undergoing posterior spinal fusion for idiopathic scoliosis: a) intra-operative blood loss and b) total blood loss.

**Table III.** Laboratory and transfusion data

| Parameter* | Control group (n = 30) | Treatment (n = 30) | p-value |
|---|---|---|---|
| Haemoglobin (g/l) | | | |
| Pre-operative | 139 (11) | 138 (9.6) | 0.82 |
| Screw insertion | 117 (13) | 119 (14) | 0.61 |
| Closing | 117 (14) | 116 (15) | 0.82 |
| First post-operative day | 109 (13) | 109 (10) | 0.81 |
| Second post-operative day | 96 (11) | 101 (10) | 0.039 |
| Red blood cell infusion (n)† | | | |
| Intra-operative | 2 | 2 | 1.0 |
| Post-operative | 3 | 3 | 1.0 |
| Autologous red blood cell infusion (ml) | 123 (127) | 110 (135) | 0.71 |

* The values are given as means, with the standard deviation in parenthesis
†Number of patients receiving red blood cell infusion

group for statistical comparison on the intention-to-treat principle.[24]

## Results

**Peri-operative and transfusion data**. The baseline characteristics of the enrolled patients are shown in (Table I). The mean pre-operative major curve in the control group was 55° (45° to 75°) and was corrected to 12° (6° to 25°). The mean pre-operative major curve in the intervention group was 53° (45° to 77°) and was corrected to 13° (4° to 24°; p = 0.96). The groups were similar at baseline with one exception; the control group had significantly less correction in the main thoracic curves on bending radiographs than the treatment group (p = 0.033) (Table II). Two patients in each group received an allogeneic red blood cell transfusion during surgery and three patients in each group post-operatively (Table III). One patient in the control group received two units of gelatine matrix with thrombin during surgery based on the safety criteria (> 50% blood loss). One patient in the treatment group received more than four units of gelatine matrix with human thrombin (six units) to reduce excessive intra-operative blood loss.

**Blood loss**. Both the intra-operative blood loss and the total blood loss increased with the duration of the operation (Fig. 2, Tables III to V).

There were no statistically significant differences in the post-operative laboratory values between the study groups with one exception: the control group had significantly lower Hb and Hct values on the second post-operative day compared with the treatment group (Table III).

Due to the relationship between blood loss and duration of surgery, the effect of treatment and other risk factors on bleeding were analysed using a multiple linear regression model (Table V). Every hour of operating increased the intra-operative blood loss by a mean 356.9 ml (95% confidence interval (CI) 273 to 440) and the total blood loss by a mean 430.5 ml (95% CI 343 to 518) (Table V). After adjusting for duration of operation and number of pedicles instrumented the intervention significantly decreased the intra-operative (-171 ml, 95% CI -320 to -22, p = 0.025) and total blood loss (-177 ml, 95% CI -333 to -21, p = 0.027) compared with that of the control group (Table V).

The decrease in haemoglobin concentration from the day before surgery to the second post-operative day was further

**Table IV.** Blood loss and operating time in the control and treatment groups

| Parameter* | Control (n = 30) | Treatment (n = 30) | p-value |
|---|---|---|---|
| Blood loss (mls) | 597 (410) | 533 (475) | 0.57 |
| % of blood volume | 16 (10) | 14 (14) | 0.60 |
| Per level | 54 (37) | 45 (37) | 0.40 |
| Per screw | 28 (24) | 24 (19) | 0.40 |
| Per degree | 11 (6.0) | 9.6 (7.3) | 0.60 |
| Drain output (mls) | 513 (169) | 532 (151) | 0.64 |
| % of blood volume | 14 (5.2) | 14 (5.1) | 0.91 |
| Per level | 46 (13) | 47 (13) | 0.77 |
| Per screw | 23 (6.8) | 24 (6.9) | 0.62 |
| Per degree | 9.5 (3.3) | 10 (2.7) | 0.33 |
| Total blood loss (mls)† | 1110 (459) | 1065 (563) | 0.74 |
| % of blood volume | 29 (12) | 28 (18) | 0.70 |
| Per level | 100 (40) | 92 (44) | 0.51 |
| Per screw | 52 (26) | 48 (22) | 0.54 |
| Per degree | 20 (7.0) | 20 (8.2) | 0.94 |
| Operating time (hrs) | 3.0 (0.80) | 3.3 (1.1) | 0.25 |
| Per level | 0.27 (0.072) | 0.29 (0.086) | 0.42 |
| Per screw | 0.14 (0.047) | 0.15 (0.043) | 0.45 |
| Per degree | 0.054 (0.011) | 0.062 (0.016) | 0.039 |

*The values are given as means, with the standard deviation in parenthesis.
† Total blood loss consisted of the intra-operative blood loss and the drain output over 24 hours post-operatively.

**Table V.** Multivariate analyses on the effect of gelatine matrix with human thrombin on intra-operative, total blood loss, and post-operative decrease in haemoglobin concentration*

| Risk factor | Intra-operative blood loss | | | Total blood loss | | | Post-operative decrease in haemoglobin concentration | | |
|---|---|---|---|---|---|---|---|---|---|
| | β (mls) | 95% CI | p-value | β (mls) | 95% CI | p-value | β (g/l) | 95% CI | p-value |
| Pedicles instrumented (blood loss or haemoglobin decrease per pedicle) | 19.7 | -37.6 to 77.1 | 0.49 | 35.6 | -24.5 to 95.7 | 0.24 | 2.6 | 0.7 to 4.5 | 0.008 |
| Operating time (blood loss or haemoglobin decrease per hour) | 356.9 | 273 to 440 | < 0.001 | 431 | 343 to 518 | < 0.001 | 1.9 | -0.7 to 4.5 | 0.15 |
| Intervention | -171 | -320 to -22 | 0.025 | -177 | -333 to -21 | 0.027 | -6.0 | -10.7 to -1.3 | 0.013 |

* Analysed with multiple linear regression model
CI, confidence interval

characterised by the multiple linear regression model. The duration of operation did not significantly affect the decrease in Hb, but every pedicle instrumented decreased the post-operative Hb by 2.6 g/l (Table V). The addition of gelatine matrix with human thrombin significantly reduced the decrease in the post-operative Hb by 6 g/L (Table V).

**Length of stay and complications**. The length of stay in hospital was similar in both groups (7.1 *vs* 7.3 days, p = 0.53). No adverse effects related to use of gelatine matrix with human thrombin were reported and there was no acute deep wound infections or neurological deficits in either group.

## Discussion

In accordance with the previous findings of Renkens et al[13] on faster surgical haemostasis with thrombin based sealant, we demonstrate here that the use of gelatine matrix with human thrombin decreases both the intra- and post-operative blood loss when added to traditional means to address surgical bleeding in adolescents undergoing surgery for idiopathic scoliosis.

The mean post-operative drainage was slightly greater in the intervention group than in the control group, although small differences in the basic demographic variables such as BMI and the inclusion of more Lenke 6 curves may have contributed to this. However, when adjusted for the number of pedicles instrumented and the duration of operation, the treatment group had a mean of 6 ml less blood loss post-operatively. It is therefore possible that gelatine matrix may decrease the continuing post-operative blood loss from exposed and decorticated posterior spinal elements and / or the epidural space, as the treatment group also in our study had significantly higher Hb and Hct values on the second post-operative day.

A halo effect is a possible confounding factor in randomised controlled studies. The haemostasis in the control group may be better than normal, which may also reduce the observed differences between the study groups.

Orthopaedic surgeons who undertake surgery for spinal deformity need to consider whether the product is cost effective as well as reflecting on possible adverse effects such as anaphylaxis.[17,18] One patient in the control group

was given gelatine matrix with thrombin to address an intra-operative blood loss of > 50% of the circulating volume. Given that a similar number of patients in both groups received allogeneic blood transfusions, the average additional cost of gelatine matrix used per patient would be £11 in the control group and £575 in the treatment group.

There are risks of using the cell saver with gelatine matrix.[30] Gelatine matrix with human thrombin should not be drained directly into the cell saver. Despite irrigation, fragments of gelatine matrix may enter through the transfusion filters of the blood scavenging systems and become mixed with the autologous blood. Blood from the cell saver should also be transfused slowly to reduce the risk of anaphylaxis.

In conclusion, the use of gelatine matrix with human thrombin reduces both intra-operative blood loss and the post-operative decrease in haemoglobin concentration in adolescents undergoing surgery for idiopathic scoliosis when added to conventional methods of addressing blood loss. Based on the current findings, we recommend its use in adolescents undergoing posterior spinal fusion for idiopathic scoliosis.

**Author contributions:**
I. Helenius: Data collection, performed surgeries, writing the paper.
H. Keskinen: Data collection, data analysis, writing the paper.
J. Syvänen: Data collection, data analysis, writing the paper.
H. Lukkarinen: Data analysis, writing the paper.
M. Mattila: Performed surgeries, writing the paper.
J. Välipakka: Performed surgeries, writing the paper.
O. Pajulo: Performed surgeries, writing the paper.

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